From: "John L. O'Donoghue"
To: <coshita@oehha.ca.gov>
CC: "'CARLTON, Betsy'"
Date: 4/28/2009 8:43 AM
Subject: Comments Submitted for the May 29, 2009 CIC meeting
Attachments: Comments on OEHHA Summary for Hydroquinone_2009_4_28.pdf; DeCaprio_1999.pdf; Whysner et al_1995.pdf

Dear Dr. Oshita:

Attached is a set of comments submitted by the Hydroquinone Group for the May 2, 2009 CIC meeting. We appreciate this opportunity to provide comments to you and to the CIC for consideration at the meeting. If you have comments about this submission or about hydroquinone in general, please feel free to contact me. I would appreciate it if you would acknowledge receipt of this transmission so that I know that you received it in good condition.

Sincerely,

John L. O'Donoghue, VMD, PHD, DABT

Scientific Advisor and Group Manager

Hydroquinone Group

3915 Clover Street

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--- Scanned by M+ Guardian Messaging Firewall ---

April 28, 2009

Via Electronic Mail

Dr. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010 1001 I Street, 19th floor
Sacramento, California 95812-4010

Subject: Comments on the March 2009 OEHHA Summary Document for Hydroquinone to be Reviewed at the May 29, 2009 Carcinogen Identification Committee Meeting

Dear Dr. Oshita:

The Hydroquinone Group[1] appreciates the opportunity to provide comments to the Carcinogen Identification Committee (CIC) for its deliberations on hydroquinone at its May 29, 2009 meeting.

Our comments on the March 2009 OEHHA Summary Document for Hydroquinone that was distributed to the CIC are summarized in the following bullet points and expanded upon in the attachment.

- The introductory paragraph does not provide an accurate view of the potential for exposure to manufactured hydroquinone as it confuses uses in which hydroquinone itself is used with those in which derivatives of hydroquinone are used.
- Of the cohort studies available for hydroquinone or combined hydroquinone and p-benzoquinone exposure, none demonstrate a significant risk of carcinogenicity.
- The scientific literature presented for review by the CIC includes none of the original health effects studies on the species-specific differences in the mammalian response to hydroquinone, the greater sensitivity of the male F344 rat kidney to hydroquinone, and mode-of action of hydroquinone. An overview of this information is provided by our comments. The article by McGregor (2007) in the reference list provided by OEHHA to the CIC provides significant detail on the mode-of action of hydroquinone.
- The studies cited in the summary document do not include the available research that shows exposure of experimental animals to hydroquinone, like other monophenolics, is associated with anticarcinogenic effects.
- Overall, the evidence for genotoxicity *in vivo* for hydroquinone is sparse and none has been observed in kidney which is a target organ for the male F344 rat.
- The studies cited in the summary document do not include the available research that shows exposure of experimental animals to hydroquinone is associated with antimutagenic effects.

[1] The HQ Group is comprised of major global manufacturers of hydroquinone.

- Although hydroquinone is one of the many metabolites of benzene, no study with hydroquinone or mixtures of hydroquinone with other benzene metabolites has been able to reproduce the toxic or carcinogenic effects of benzene.
- Simplistic structure-activity comparisons of hydroquinone with benzene or catechol are not supported by comparing and contrasting the bioassay results of hydroquinone, benzene, and catechol as the hydroquinone bioassay results are in sharp contrast to the results of the bioassays for benzene and catechol.
- There are four extensive reviews of hydroquinone that are not identified in the Summary Document.

We are also providing attachments that include two of the review articles on hydroquinone. If requested, we can provide copies of the references cited in our comments.

Based on the large database available on hydroquinone and particularly mechanistic studies demonstrating that the mode-of-action for hydroquinone in the F344 rat is not relevant for humans, we do not think that hydroquinone should be a high priority for preparation of Hazard Identification Materials.

Please feel free to contact us if you have any questions regarding this submission or on hydroquinone, in general.

Sincerely,

John L. O'Donoghue (es)

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Comments on the Summary Document for Hydroquinone to be Reviewed at the May 29, 2009 Carcinogen Identification Committee Meeting

1.0 Introductory Paragraph

1.1 The introductory paragraph does not provide an accurate view of the potential for exposure to manufactured hydroquinone as it confuses uses in which hydroquinone is used with those in which derivatives of hydroquinone are used.

Hydroquinone is both a manufactured and a naturally occurring antioxidant. According to the Organisation for Economic Cooperation and Development (OECD, 2000), virtually all uses of manufactured hydroquinone are industrial (>95%). Many of these industrial uses are non-dispersive and result in the consumption of hydroquinone leading to no or very little exposure.

The introductory paragraph is incomplete in the way in which it describes the uses of hydroquinone as it confuses uses where there may be potential exposure to hydroquinone with uses where there is no potential for exposure to hydroquinone. For example, the summary document is incorrect when it states that, "It is used as …an antioxidant and antiozonate for rubber…." Rather, hydroquinone is used as an intermediate for synthesis of antioxidants and antiozonants for use in rubber. Other similar uses for hydroquinone include chemical conversion of hydroquinone to products used as stabilizers for paints, varnishes, motor oils, and fuels.

While the summary document is correct in identifying hydroquinone use in the imaging industry including black-and-white photographic film, lithography, and hospital x-ray film, these imaging uses of hydroquinone are sharply declining due to a technical shift away from chemical processing of film to digital media which do not require hydroquinone for processing.

2.0 Occupational Cohort Studies:

2.1 Of the cohort studies available for hydroquinone or combined hydroquinone and p-benzoquinone exposure, none demonstrate a significant risk of carcinogenicity.

Of the occupational cohort studies available for hydroquinone, the study by Pifer *et al.* (1995) is the most complete as it not only has extensive industrial hygiene data, and significant exposure and latency periods, it also includes an industrial control population to address the issue of the healthy worker effect. The other significant feature in this study is that there was co-exposure to p-benzoquinone which is metabolite of hydroquinone.

The Pifer *et al*. (1995) cohort mortality study included 879 workers (22,895 person–years of follow-up) at a plant in which hydroquinone was manufactured on a full-time basis and used over several decades. A prior study (Pifer *et al*., 1986) had reported a statistically significant decrease in standardized mortality ratio from all causes among employees of the organic chemicals division where hydroquinone was produced. Cohort members had at least six months of exposure between January 1930 and December 1990. Job histories were linked to extensive industrial hygiene data to estimate cumulative exposures to hydroquinone and p-benzoquinone. Mean hydroquinone levels ranged from 0.1 to 6.0 mg/m^3 dust, with levels over 2 mg/m^3 for the period up to 1964. Mean exposure duration was 13.7 years. The mean follow-up period from first exposure was 26.8 years. Relative risk estimates (standardized mortality ratios or SMRs) for the hydroquinone cohort were determined by comparison with the general population of the State of Tennessee and to an occupational cohort without hydroquinone or p-benzoquinone exposure. The SMRs for all causes of death combined and all cancers combined were significantly less than 1 and most site-specific SMRs were below 1.0 as well. Similar results were observed in comparison to both control populations. The population of hydroquinone-exposed workers in this study represents the vast majority of all hydroquinone manufacturing workers in North America during the time period covered by the epidemiology study.

Nielsen *et al*. (1996) conducted a cohort incidence study among 620 Danish lithographers who answered a questionnaires sent to obtain information on job exposures. A total of 24 cancers for this cohort were located in the Danish Cancer registry providing a Standard Incidence Ratio (SIR) of 0.9 when compared to the general Danish population. Five cases of malignant melanoma occurred among the lithographers with 1.5 expected; however, only 2 of the 5 lithographers reported exposure to hydroquinone indicating no significant relationship to hydroquinone exposure.

Frysek *et al*. (2005) reported a retrospective cohort mortality study of 2646 workers engaged in motion picture film processing at a California laboratory for at least three months. A borderline significant excess of non-Hodgkin lymphoma was observed among hourly workers (SMR = 2.2), a borderline significant excess of malignancies of the respiratory system was reported for all workers combined (SMR = 1.3). A significant excess of respiratory malignancies was observed in the developing group (SMR = 1.9); but, based on duration of exposure, there was no relationship between exposure and the observed excess malignancies. Workplace air monitoring for hydroquinone reported levels of < 0.014 and 0.052 mg/m^3.

Likewise in a study reported by Friedlander *et al*. (1982) of color print and processing employees, no significant adverse effects were noted, but exposures to hydroquinone were low.

3.0 Animal Carcinogenicity Data

3.1 The scientific literature presented for review by the CIC includes none of the original health effects studies on the species-specific differences in the mammalian response to hydroquinone, the anomalous greater sensitivity of the male F344 rat kidney to hydroquinone, and mode-of action of hydroquinone. The following paragraphs provide an overview of this information which is also discussed in more detail in McGregor (2007) which details the mode-of-action of hydroquinone and the lack of relevance of the tumors seen in the F344 rat for human health.

Hydroquinone has been tested for carcinogenicity in two studies in mice and two studies in rats by oral administration using gavage and dietary administration as means of exposure. It has also been tested in several studies in rats for carcinogen promoting activity in assays for bladder, stomach, liver, lung, esophagus, and kidney carcinogenesis and in one study in Syrian hamsters for pancreatic carcinogenesis. The lack of carcinogenicity in most of these studies of promotion is discussed in McGregor (2007).

In mice, hydroquinone exposure was associated with hepatocellular adenomas in females in one study and in males in another study (NTP, 1989; Shibata *et al*., 1991). In rats, hydroquinone induced renal tubule adenomas in males in two studies. In none of the experiments with hydroquinone was there an increased incidence of malignant neoplasms that was related to treatment. The only consistent neoplasm that has been observed in animal studies is renal tubule cell adenoma in male F344 rats. The renal tubule cell adenomas were present in rats that concurrently showed exacerbation of spontaneous chronic progressive nephropathy (CPN) (Hard *et al.*, 1997). The exacerbation of CPN was associated with chronic nephrotoxicity induced by hydroquinone in the male F344 rats.

All of the available data demonstrate that male F344 rats display a greater sensitivity to nephrotoxicity of hydroquinone than do other species and strains of rat, including female F344 rats, Sprague-Dawley (SD) rats, and $B6C3F_1$ mice (National Toxicology Program, 1989; Shibata *et al*., 1991; Carlson and Brewer, 1953; Boatman *et al*., 1996; Topping *et al*., 2007). Exacerbation of CPN by hydroquinone was not as pronounced in female rats, and nephrotoxicity was not observed in male SD rats. Significant increases in renal tubular cell adenomas over controls were also not found in female F-344 rats, male SD rats, or male or female $B6C3F_1$ mice.

The mode of action for the induction of nephrotoxicity and renal tubule cell adenomas has been studied extensively to understand whether the F344 rat data are relevant for human health. Renal toxicity in the male F344 rat following hydroquinone exposure has been associated with the glutathione conjugation biotransformation pathway.

Following oral exposure, hydroquinone is conjugated in the intestinal mucosa and liver to glucuronic acid and sulfate conjugates, and excreted rapidly in the urine

(DiVincenzo *et al.*, 1984). Pulmonary absorption and clearance after intratracheal instillation is also very rapid (Deisinger and English, 1999).

A small percentage of orally administered hydroquinone is excreted in the urine as the mercapturic acid conjugate (English and Deisinger, 2005) indicating the intermediate formation of the glutathione and cysteine conjugates. The mono-S-glutathione conjugate, as well as di- and tri-substituted glutathione conjugates have been identified in the bile after intraperitoneal administration (Hill et al., 1993, 1994).

In the kidney, the brush border enzyme gamma-glutamyl transpeptidase (GGT) acts on glutathione conjugates producing one equivalent of L-glutamate plus the corresponding cysteinyl-glycine conjugate (Elfarra and Anders, 1984; Monks and Lau, 1990; Anders *et al.*, 1992; Dekant, 1993). Dipeptide conjugates are in turn hydrolyzed by a poorly defined dipeptidase to yield L-glycine plus the corresponding cysteine conjugate, (L-cystein-*S*-yl) hydroquinone (CysHQ) in this case. Intravenous administration of the glutathione conjugates of HQ cause nephrotoxicity, and inhibition of GGT by treatment with acivicin protected against this effect (Lau *et al.*, 1988).

These findings have led to the belief that glutathione conjugates of hydroquinone formed within the liver are further bioactivated to cysteine conjugates, the proximate nephrotoxic species in the male F344 rat. The *N*-acetylation reaction to form the mercapturic acid, (N-acetyl-L-cystein-*S*-yl)hydroquinone (*N*-AcCysHQ), represents a detoxification, and competes with oxidative reactions for the CysHQ substrate. These oxidative reactions, possibly catalyzed by peroxidases and/or cytochrome P-450, produce quinone metabolites that bind covalently to S-proteins (Kleiner, *et al*., 1998; Boatman *et al*., 2000 a and b). Single electron oxidation of quinone metabolites is expected to yield the semiquinone radical anion and active oxygen species, which may contribute to tissue damage by oxidizing macromolecules in the male F344 rat (DeCaprio, 1999).

Biotransformation of hydroquinone via glutathione conjugation and mercapturate formation is catalyzed by enzymes that have been demonstrated to have tissue, sex, strain, and species differences. Physiologically-based pharmacokinetic modeling of hydroquinone metabolism and direct comparison between rat and human metabolic parameters using an *in vitro* hepatocyte model suggested a greater flux of hydroquinone through the bioactivation pathway only in the male F344 rat (Corley *et al*., 2000; Poet *et al.,* 2004). In the most recent investigation of the metabolism of hydroquinone, Barber and English (2009) used *in vitro* subcellular tissue fractions to evaluate the rates of CysHQ detoxification by rodent and human kidney. The primary purpose of these studies was to measure the specific activity of *N*-acetylation of CysHQ and *N*-deacetylation of *N*-AcCysHQ in kidney subcellular fractions of male and female F344 rats, male SD rats, and male B6C3F$_1$ mice, and to determine if any differences in these activities correlate with the established toxicities of hydroquinone in the corresponding in

vivo test systems. The significantly lower rate of acetylation in the male F344 rat compared with the female F344, male SD rat, or the male mouse, suggests that the male F344 rat has an inferior capacity for detoxification of CysHQ. This, in turn, may contribute to the chronic effects of hydroquinone observed in the male F344 rat but not the other animal models or humans.

As noted above, the nephrotoxic and carcinogenic effects observed in the male F344 rat have not been observed in humans. Sterner, *et al*. (1947) performed clinical and laboratory evaluations on 88 employees in 1943 and on 101 employees in 1945 who worked in a large hydroquinone manufacturing plant where there was dermal and airborne exposure to hydroquinone dust and p-benzoquinone vapor for periods of up to 15 years. No systemic toxicity was evident in the workers; although the exposures were high enough to cause corneal changes in the eyes of some of the workers.

As part of a controlled study, two men ingested 500 mg/day of hydroquinone for 5 months and 17 volunteers (men and women) ingested 300 mg/day of hydroquinone for 3-5 months without pathological changes in their hemogram or urine (Carlson and Brewer, 1953). Pifer *et al*. (1995) studied a population of 858 men and 21 women in a 1942-1990 cohort of employees involved in manufacturing and using hydroquinone on a daily basis. The 8-hr time-weighted average exposure to hydroquinone dust in the workplace was 0.1 - 6.0 mg/m^3 and 0.1 - 0.3 ppm for p-benzoquinone vapor. These exposures included skin contact with hydroquinone as the work process involved manually filling bags with hydroquinone. No evidence of deaths due to renal toxicity or kidney cancer was observed in this study.

These studies demonstrate that the male F344 rat has a unique sensitivity to hydroquinone that is not shared with humans and provide a basis for a mechanistic understanding of why the results of the cancer bioassay in the F344 rat are not relevant for humans.

3.2 The studies cited in the summary document do not include research demonstrating that exposure of experimental animals to hydroquinone, like other monophenolics, is associated with anticarcinogenic effects.

Monocyclic phenolic compounds including acetaminophen, butylated hydroxyanisole, and butylated hydroxytoluene have been demonstrated to have anticarcinogenic properties in animal models of liver and colon cancer (Williams *et al*., 2002). In a study to determine if hydroquinone had similar properties, groups of male F344 rats were fed daily diets at either 0.05% HQ (~25 mg/kg bw/d) or 0.2% HQ (~100 mg/kg bw/d) for 13 weeks, starting one week before the hepatic carcinogen 2-acetylaminofluorene (AAF) was administered, and at the same dose levels to 2 groups of rats not receiving AAF (Williams *et al*., 2007). AAF was given intragastrically at dose level of 3 mg/kg bw. A vehicle control group was administered 0.5% carboxymethyl cellulose intragastrically 3 times a

week. At the end of the study, DNA adducts (^{32}P postlabeling), cell proliferation (PCNA immunohistochemistry) and preneoplastic hepatocellular altered foci (HAF) (glutathione S-transferase-placental type immunohistochemistry) were measured. At the low dose level of hydroquinone, adduct levels induced by AAF were 90% of that for AAF alone, whereas at the high HQ dose level, AAF adducts were reduced by 33% ($p<0.05$). AAF exposure yielded about a 50% increase in hepatocellular proliferation and both hydroquinone dose levels reduced the AAF-induced increases in proliferation by about 25%. Likewise, the AAF-induced GST-P positive HAF per cm^2 of liver tissue were decreased by both dose levels of hydroquinone by about 50%. Thus, at both 0.05% and 0.2% hydroquinone in the diet, diminished AAF-induced cancer initiating effects in rat liver were observed.

4.0 Genotoxicity

4.1 Overall, the evidence for genotoxicity *in vivo* for hydroquinone is sparse and none has been observed in kidney which is a target organ for the male F344 rat.

The mutagenicity data for hydroquinone has been summarized by IPCS (1994), Whysner *et al.* (1995), IARC (1999), and most recently by McGregor (2007). In most studies of bacterial mutagenesis such as the Ames/Salmonella test hydroquinone has not shown signs of genotoxicity while in many *in vitro* tests of DNA interaction such as DNA binding, strand breaks and repair, and DNA replication, largely positive results have been reported (Whysner *et al*., 1995). The most consistent effect seen with hydroquinone has been the induction of chromosomal aberrations and aneuploidy when tested *in vitro* or *in vivo* by parenteral routes of exposure (Whysner *et al.*, 1995). However, recent studies of human lymphocytes exposed *in vitro* to hydroquinone have not shown chromosomal effects (Doepker *et a*l., 2000; Roza *et al*., 2003). As reviewed below by McGregor (2007), *in vivo* studies of hydroquinone genotoxicity included only three studies in which dose routes other than the intraperitoneal or subcutaneous routes were used. These were a Swiss mouse bone marrow cell micronucleus test in which a marginally positive response was obtained following a single oral dose of 80 mg/kg bw, a second Swiss mouse micronucleus test in which there was no genotoxic activity after exposure to a diet containing 0.8% HQ for six days and two DNA binding assays, one study with Sprague-Dawley rats in which no adducts were found in Zymbal's gland, liver or spleen, following four oral doses of 150 mg/kg bw, and one study with male F344 rats in which no adducts were found in kidney, following five daily oral doses of 50 mg/kg bw for six weeks (English *et al*. (1994 a and b). Overall, the evidence (and the database) for any genotoxic effect *in vivo* for HQ is sparse and none has been observed in the kidneys.

4.2 The studies cited in the summary document do include research demonstrating that exposure of experimental animals to hydroquinone is associated with antimutagenic effects.

The ability of HQ to prevent mutagenicity by a route of exposure other than parenteral was examined in rats fed diets containing 0.8% HQ (O'Donoghue *et al*., 1999). In these studies, a 0.8% HQ diet fed for six days did not induce micronuclei and reduced the background incidence of micronuclei in HQ-exposed animals. This diet also reduced the induction of micronuclei by 36% in rats given $KBrO_3$, a known inducer of micronuclei. Administration of a single dose of 50 mg/kg HQ by oral gavage also reduced the micronucleus response induced by intraperitoneal injection of 50 mg/kg $KBrO_3$.

5.0 Metabolite of a Carcinogen and Structure Activity Comparisons

5.1 Hydroquinone is one of the many metabolites of benzene. However, no study with hydroquinone or mixtures of hydroquinone with other benzene metabolites has been able to reproduce the toxic or carcinogenic effects of benzene.

Benzene has been classified as an International Agency for Research on Cancer (IARC, 1987) Group 1 substance (carcinogenic to man) based on epidemiological evidence of an increased risk of acute myelogenous leukemia in workers exposed to it in occupational settings and on the induction of a wide range of benign and malignant tumors in male and female F-344 rats and mice (NTP, 1986). Among the numerous benzene metabolites are benzene oxide, phenol, catechol, hydroquinone, 1,2,4-benzentriol, trans-trans-muconic acid, 1-phenylmercapturic acid and the downstream metabolites of these chemicals(Snyder and Hedli, 1996). Inhibition of benzene metabolism through competitive inhibition or partial hepatectomy has been shown to reduce the hematologic toxicity of benzene (Snyder and Hedli, 1996). Hence, the metabolites of benzene were thought to be important in the induction of its toxicity including carcinogenicity. Numerous studies have been completed with hydroquinone or combinations of hydroquinone with other benzene metabolites but none of these studies has been able to reproduce the toxicity seen following benzene exposure. A likely significant reason for this difference is that site specific metabolism of benzene plays a critical role in its toxicity and carcinogenicity. The site specific metabolism of benzene is a consequence of its fat solubility which causes it to have a different pattern of distribution and half-life in the body as compared to substances such as hydroquinone which are water soluble.

5.2 Simplistic structure-activity comparisons of hydroquinone with benzene or catechol are not supported by comparing and contrasting the bioassay results of hydroquinone, benzene, and catechol as the hydroquinone bioassay results are in sharp contrast to the results of the bioassays for benzene and catechol.

Table 1 outlines the significant contrasting effects seen in the bioassays conducted with hydroquinone, benzene, and catechol. The bioassays for these chemicals were conducted using very similar test protocols. Exposure to benzene impaired survivability, consistently induced lymphopenia, induced hyperplasic responses in some organs, and induced multiple types of benign and malignant tumors in male and female rats and mice. Consequently IARC considered these data sufficient to classify benzene as an animal carcinogen. In conjunction with human epidemiology, the International Agency for Research on Cancer (IARC) classified benzene as a Group 1 human carcinogen. In contrast, the chronic toxicity and bioassay results for hydroquinone do not significantly overlap with effects in rodents seen after benzene exposure. None of the bioassay results were considered clear evidence of carcinogenicity in rats or mice and IARC has classified hydroquinone as a Group 3 material or as not classifiable for carcinogenicity. IARC has also classified p-benzoquinone, a metabolite of hydroquinone as a Group 3 material. Similarly (as shown on Table 1), the bioassay results for catechol do not overlap with those of benzene or hydroquinone.

6.0 Reviews

6.1 There are four extensive reviews of hydroquinone that are not identified in the Summary Document.

These include the following articles two of which are being sent as attachments to these comments.

DeCaprio, A. P. (1999). The toxicology of hydroquinone - relevance to occupational and environmental exposure. *Critical Reviews in Toxicology* **29,** 283-330.

Whysner, J., Verna, L., English, J.C., and Williams, G. M. (1995). Analysis of studies related to tumorigenicity induced by hydroquinone. *Regulatory Toxicology and Pharmacology* **21**, 158-176.

The other reviews are available on the internet as indicated below.

International Programme on Chemical Safety (IPCS). (1994). Environmental Health Criteria 157: Hydroquinone. World Health Organization, Geneva. Available at: http://www.inchem.org/documents/ehc/ehc/ehc157.htm.

Organisation for Economic Cooperation and Development. (2000). OECD SIDS Initial Assessment Profile on 1,4-Benzenediol (Hydroquinone). Available at: http://cs3-hq.oecd.org/scripts/hpv/index.asp.

Table 1: Comparison of Bioassays for Hydroquinone, Benzene, and Catechol

	NTP Hydroquinone Bioassay **NTP, 1989**	**NTP Benzene Bioassay** **NTP, 1986**	**Catechol** **IARC Vol 71, 1999**
Species and strain	F344/N rats and B6C3F$_1$ mice	F344/N rats and B6C3F$_1$ mice	F344 rats and B6C3F$_1$ mice
Exposure route and dose	25 and 50 mg/kg Oral gavage	50, 100, and 200 mg/kg-male rats 25, 50, 100 mg/kg all other grps. Oral gavage	0.8% in the diet
Survival	No significant effect	Dose-dependent dec. all groups	No significant effect
Toxicity observed			
Male rats	Exacerbation of chronic progressive nephropathy	Lymphocytopenia, lymphoid depletion of spleen and thymus	Reduced bodyweight, Increased liver weight, forestomach hyperplasia, adenomatous hyperplasia of glandular stomach
Female rats	Red blood cells changes	Lymphocytopenia, lymphoid depletion of spleen,	Reduced body weight, forestomach hyperplasia, adenomatous hyperplasia of glandular stomach
Male mice	Hepatic cellular changes and thyroid follicular cell hyperplasia	Lymphocytopenia; hyperplasia bone marrow, capsule and zona fasiculata of the adrenal gland;	Reduced body weight, adenomatous hyperplasia of glandular stomach
Female mice	Thyroid follicular cell hyperplasia	Lymphocytopenia; hyperplasia of the bone marrow, and capsule and zona fasiculata of the adrenal gland;	Reduced body weight, adenomatous hyperplasia of glandular stomach
Tumor type (s) observed			
Male rats	Renal tubular adenoma	Zymbal gland carcinoma, squamous cell tumors of skin and oral cavity	Papilloma in forestomach, adenocarcinoma of glandular stomach
Female rats	Mononuclear cell leukemia	Zymbal gland carcinoma squamous cell tumors of the oral cavity	Adenocarcinoma of glandular stomach
Male mice	None	Zymbal gland carcinoma, squamous cell tumors, malignant lymphoma, lung tumors, Harderian gland tumors, preputial gland tumors	None
Female mice	Hepatocellular tumors, primarily adenomas	Zymbal gland carcinoma, squamous cell tumors, malignant lymphoma, lung tumors, mammary tumors, ovarian tumors	None
IARC Classifications			
IARC Evaluation of Animal Data	Limited evidence of carcinogenicity	Sufficient evidence of carcinogenicity	Sufficient evidence of carcinogenicity
IARC Overall Evaluation	Group 3: Not classifiable	Group 1: carcinogenic to humans	Group 2B: possibly carcinogenic to humans

7.0 References

Anders, M.W., Dekant, W., and Vamvakas, S. (1992). Glutathione-dependent toxicity. *Xenobiotica* **22** 1135-1145.

Barber, E.D. and English, J.C. (2009). Comparison of the Rates of Interconversion of (L-cystein-*S*-YL)-hydroquinone and (*N*-acetyl-L-cystein-*S*-YL) hydroquinone in male and female Fischer 344 rat, male Sprague-Dawley rat, male B6C3F$_1$ mouse, and human kidneys. *To be submitted for publication*.

Boatman, R. J., English, J. C., Perry, L. G., and Bialecki, V. E. (1996). Differences in the nephrotoxicity of hydroquinone among Fischer 344 and Sprague-Dawley Rats and B6C3F$_1$ mice. *Journal of Toxicology and Environmental Health* **47**, 159-172.

Boatman, R.J., English, J.C., Perry, L.G., and Fiorica, L.A. (2000a). Covalent protein adducts of hydroquinone in tissues from rats: identification and quantitation of sulfhydryl-bound forms. *Chemical Research in Toxicology* **13**, 853-860.

Boatman, R. J., English, J. C., Perry, L. G., and Fiorica, L. A. (2000b). Covalent protein adducts of hydroquinone in tissues from rats: Quantitation of sulfhydryl-bound forms following single gavage or intraperitoneal administration or repetitive gavage administration. *Chemical Research in Toxicology* **13**, 861-872.

Carlson, A.J. and Brewer, N.R. (1953). Toxicity studies on hydroquinone. *Proceedings of the Society for Experimental Biology and Medicine* **84,** 684-688.

Corley, R. A., English, J. C., Hill, T. S., Fiorica, L. A., and Morgott, D. A. (2000). Development of a physiologically based pharmacokinetic model for hydroquinone. *Toxicology and Applied Pharmacology* **165** 163-174.

DeCaprio, A. P. (1999). The toxicology of hydroquinone - relevance to occupational and environmental exposure. *Critical Reviews in Toxicology* **29,** 283-330.

Deisinger, P. J. and English, J. C. (1999). Bioavailability and metabolism of hydroquinone following intratracheal instillation in male rats. *Drug Metabolism and Disposition* **27,** 442-448.

Dekant, W. (1993). Bioactivation of nephrotoxins and renal carcinogens by glutathione *S*-conjugate formation. *Toxicology Letters* **67**, 151-160.

DiVincenzo, G.D., Hamilton, M.L., Reynolds, R.C. and Ziegler, D.A. (1984). Metabolic fate and disposition of [^{14}C]hydroquinone given orally to Sprague-Dawley rats. *Toxicology* **33**, 9-18.

Doepker, C. L., Dumont, K. W., O'Donoghue, J., and English, J. C. (2000). Lack of induction of micronuclei in human peripheral blood lymphocytes treated with hydroquinone. *Mutagenesis* **15**, 479-487.

Elfarra, A.A., and Anders, M.W. (1984). Renal processing of glutathione conjugates. Role in nephrotoxicity. *Biochemical Pharmacology* **23**, 3729-3732.

English, J.C., Perry, L.G., Vlaovic, M., Moyer, C., and O'Donoghue, J.L. (1994a). Measurement of cell proliferation in the kidneys of Fischer 344 and Sprague-Dawley rats after gavage administration of hydroquinone. *Fundamental and Applied Toxicology* **23**, 397-406.

English, J. C., Hill, T., O'Donoghue, J. L., and Reddy, M. V. (1994b). Measurement of nuclear DNA modification by ^{32}P-postlabeling in the kidney of male and female Fischer 344 rats after multiple gavage doses of hydroquinone. *Fundamental and Applied Toxicology* **23**, 391-396.

English, J. C. and Deisinger, P. J. (2005). Metabolism and disposition of hydroquinone in Fischer 344 rats after oral or dermal administration. *Food and Chemical Toxicology* **43**, 483-493.

Friedlander, B.R., Hearne, F.T. and Newman, B. (1982). Mortality, cancer incidence, and sickness-absence in photographic processors: and epidemiologic study. *Journal of Occupational Medicine* **24**, 605-613.

Fryzek, J.P., Chadda,B.K., Cohen, S.S., Marano, D., White, K., Steinwandel, M. and McLaughlin, J.K. (2005). Retrospective Cohort Mortality Study of Workers Engaged in Motion Picture Film Processing *Journal of Occupational and Environmental Medicine*, **47**:278–286.

Hard, G. C., Whysner, J., English, J. C., Zang, E., and Williams, G. M. (1997). Relationship of hydroquinone-associated rat renal tumors with spontaneous chronic progressive nephropathy. *Toxicologic Pathology* **25**, 132-143.

Hill BA, Kleiner HE, Ryan EA, Dulik DM, Monks TJ, Lau SS. (1993) Identification of multi-S-substituted conjugates of hydroquinone by HPLC-coulometric electrode array analysis and mass spectroscopy. *Chemical Research in Toxicology* **6,** 459-469.

Hill, B.A., Davison, K.L., Dulik, D.M., Monks, T.J., and Lau, S.S. (1994). Metabolism of 2-(glutathion-*S*-yl)hydroquinone and 2,3,5-(triglutathion-*S*-

yl)hydroquinone in the *in situ* perfused rat kidney: relationship to nephrotoxicity. *Toxicology and Applied Pharmacology* **129**, 121-132.

International Agency for Research on Cancer (IARC). (1999). Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. Volume 71 Part 2 In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, World Health Organization, Lyon.

International Agency for Research on Cancer (IARC). (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Benzene Supplement 7, (http://www-cie.iarc.fr/htdocs/monographs/suppl7/benzene.html).

International Programme on Chemical Safety (IPCS). (1994). Environmental Health Criteria 157: Hydroquinone. World Health Organization, Geneva. Available at: http://www.inchem.org/documents/ehc/ehc/ehc157.htm.

Kleiner, H.E., Rivera, M.I., Pumford, N.R., Monks, T.J., Lau, S.S. (1998). Immunochemical detection of quinol-thioether-derived protein adducts. *Chemical Research in Toxicology* **11**, 1283-1290.

Lau, S.S., Hill, B.A., Highet, R.J., and Monks, T.J. (1988). Sequential oxidation and glutathione addition to 1,4-benzoquinone: correlation of toxicity with increased glutathione substitution. *Molecular Pharmacology* **34**, 829-836.

McGregor, D. (2007). Hydroquinone: an evaluation of the human risks from its carcinogenic and mutagenic properties. *Critical Reviews in Toxicology,* Submitted for publication.

Monks, T.J., and Lau, S.S. (1990). Glutathione, gammaglutamyl transpeptidase, and the mercapturic acid pathway as modulators of 2-bromohydroquinone oxidation. *Toxicology and Applied Pharmacology* **103**, 557-563.

National Toxicology Program. (1986). Toxicology and carcinogenesis studies of benzene in F-344/N rats and B6C3F$_1$ mice. NIH Publication No. 86-2545, Research Triangle Park, NC: 1986.

National Toxicology Program (NTP.) (1989). Toxicology and carcinogenesis studies of hydroquinone in F-344/N rats and B6C3F$_1$ mice. NIH Publication No. 90-2821, Research Triangle Park, NC.

Nielsen, H., Henriksen, L. and Olsen, J.H. (1996). Malignant melanoma among lithographers. *Scandinavian Journal of Work and Environmental Health*, **22**, 108-111.

O'Donoghue, J. L., Barber, E. D., Hill, T., Aebi, J., and Fiorica, L. (1999). Hydroquinone: genotoxicity and prevention of genotoxicity following ingestion. *Food and Chemical Toxicology* **37**, 931-936.

Organisation for Economic Cooperation and Development. (2000). OECD SIDS Initial Assessment Profile on 1,4-Benzenediol (Hydroquinone). Available at: http://cs3-hq.oecd.org/scripts/hpv/index.asp.

Pifer, J.W., Hearne, F.T., Friedlander, B.R. and McDonough, J.R. (1986). Mortality study of men employed at a large chemical plant, 1972 through 1982. *Journal of Occupational Medicine*, **28**:438-444.

Pifer, J. W., Hearne, F. T., Swanson, F. A., and O'Donoghue, J. L. (1995). Mortality study of employees engaged in the manufacture and use of hydroquinone. *International Archives of Occupational and Environmental Health* **67**, 267-280.

Poet, T. S., Wu, H., English, J. C., and Corley, R. A. (2004). .Metabolic rate constants for hydroquinone in F344 rat and human liver isolated hepatocytes; Application to a PBPK model. *Toxicological Sciences* **82**, 9-25.

Roza, L., de Vogel, N., and van Delft, J.H.M. (2003). Lack of clastogenic effects in cultured human lymphocytes treated with hydroquinone. *Food and Chemical Toxicology* **41**, 1299-1305.

Shibata, M.-A., Hirose, M., Tanaka, H., Asakawa, E., Shirai, T., and Nobuyuki, I. (1991). Induction of renal cell tumors in rats and mice, and enhancement of hepatocellular tumor development in mice after long-term hydroquinone treatment. *Japanese Journal of Cancer Research* **82**, 1211-1219.

Snyder R. and Hedli, C.C. (1996). An overview of benzene metabolism. *Environmental Health Perspectives* **104** (Suppl. 6): 1165-71.

Sterner. J.H., Oglesby, F.L., and Anderson, B. (1947). Quinone vapors and their harmful effects. I. corneal and conjuctival injury. *Journal of Industrial Hygiene and Toxicology* **26**: 60-73.

Topping, D.C., Bernard, L.G., O'Donoghue, J.L., and English, J.C. (2007). Hydroquinone: Acute and subchronic toxicity studies with emphasis on neurobehavioral and nephrotoxic effects. *Food and Chemical Toxicology*, **45**:70-78.

Williams, G. M., Iatropoulos, M. J., Jeffrey, A. M. and Duan, J. D. (2007). Inhibition by dietary hydroquinone of acetylaminofluorene induction of initiation of rat liver carcinogenesis. *Food and Chemical Toxicology* **45**, 1620-1625.

Whysner, J., Verna, L., English, J.C., and Williams, G. M. (1995). Analysis of studies related to tumorigenicity induced by hydroquinone. *Regulatory Toxicology and Pharmacology* **21**, 158-176.